Joule Thomson Cryocoolers and Cryoablation

Chapter 2 in:

Crycoolers: Theory and Applications

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1.1 Overview of cryosurgery and cryosurgical probes

Cryosurgery is a technique for destroying undesirable tissue, such as cancers, using a freezing process. Treatments include prostate, breast and liver tumor ablation, as well as a variety of dermatological and gynecological procedures. Cryosurgery involves inserting a cryoprobe into the tissue to create the necessary cryogenic temperatures; the cryoprobe tip reaches approximately 150 K and the surgery may last anywhere from a few minutes to an hour [1]. These handheld surgical instruments must be compact and ergonomic to facilitate precise placement and to ensure the procedure is minimally invasive. Figure 1 shows the components of a particularly small cryoprobe that uses a Joule-Thomson (JT) cycle, and demonstrates the level of miniaturization available with this technology.

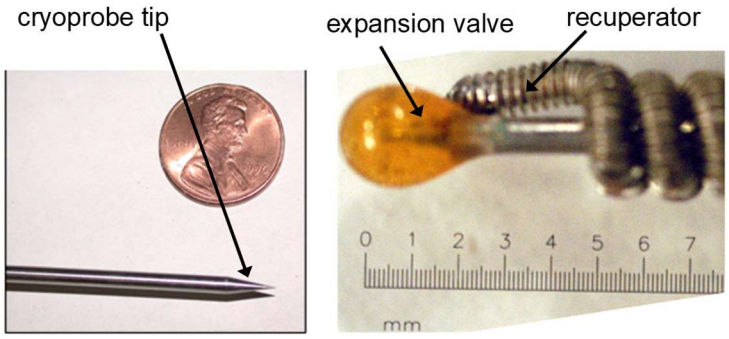

Figure -1: Photos of miniature cryoprobe components including the (a) tip and (b) the expansion valve and recuperator of a probe using a Joule-Thomson cycle.

The cryolesion (i.e. ice ball) that is formed is typically on the order of tens of millimeters in diameter, and can be enlarged by careful design of the cryoprobe cold surface area [2]. The lethal zone (i.e., the region in which cell death is complete) extends outward into the tissue from the cryo-active portion of the probe approximately to the location where the tissue

temperature is about 240 K, although this will vary by ±15 K depending on the details of the surgical procedure and location [1]. Freeze-thaw cycles are often used since both processes contribute to cell death, and the cycle is repeated to achieve complete destruction of the target tissue. The cryolesion is pear-shaped, as shown in Figure 2 (the outline of the probe has been enhanced in the figure to clarify the boundary between the probe and the ice ball). Since the affected zone extends beyond the cryoprobe point of contact, cryosurgery is an attractive option for procedures where surgical resection is not possible because of the proximity of the diseased tissue to large, healthy blood vessels; these vessels may be damaged using a more invasive technique [3].

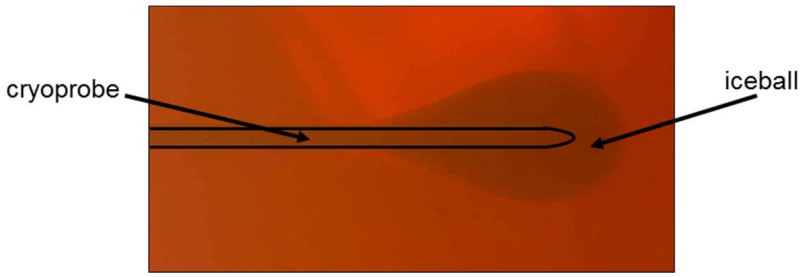

Figure 2: Photograph of an ice ball (cryolesion) grown in a gelatin solution using a cryoprobe [2].

Cryosurgical treatment of cancers began in the mid-nineteenth century when James Arnott [4] investigated the use of freezing for the treatment of cancer. Freezing tissues using a mixture of ice and various solutes had been previously used as an anesthetic, but Arnott found that freezing was also an effective treatment option for tumors in the breast and uterine cavity [1]. Advances in cryogenics over the next century led to the availability of various cryogens including liquid oxygen and liquid nitrogen, as well as solid carbon dioxide (dry ice). However, instrumentation for medical cryogen application was limited during this time and generally capable of freezing to a depth of only a few millimeters [1]. Therefore, the use of cryogenics in medicine was primarily limited to the treatment of superficial tissues in the fields of dermatology and gynecology.

Irving Cooper and Arnold Lee [5] invented the first cryosurgical probe that could produce sizable cryolesions deep within the body. Liquid nitrogen (LN2) was pumped through thin concentric tubes, evaporated by the surgical load at the tip, and then exhausted as a vapor. Liquid nitrogen cryoprobes are still used today and are attractive for their relative simplicity. The drawbacks of these systems include logistics of handling the nitrogen; the liquid nitrogen storage tanks must be periodically refilled, which limits the duration of the procedure, and the nitrogen vapor must be vented to avoid an asphyxiation hazard. Additionally, the probes and other equipment involved in transporting the liquid nitrogen to the cryoprobe must be vacuum insulated which adds complexity and can potentially make the system bulky.

The next generation of cryosurgical probes uses a pure gas (e.g., argon) in a JT refrigeration cycle. A high-pressure (often 20 MPa or 3000 psi) gas cylinder is used to provide high-pressure gas to an open-cycle JT system. The high-pressure gas expands and cools at the cryoprobe tip where it cools the tissue, passes through a recuperator that cools the incoming high-pressure gas, and finally exits the probe. The advantage of this system is

that the gas entering the cryoprobe is at room temperature and therefore vacuum insulation is not required, so these probes are much smaller than their liquid nitrogen counterparts. However, the pressures required by the single-component gas in a JT system are too large to be provided by any portable compressor and thus the need for a high-pressure gas bottle. The low-pressure gas leaving the open system is not recovered and therefore represents an asphyxiation hazard, so the medical facility must be equipped with an auxiliary ventilation system. The system consumes a large amount of gas since the cooling effect per unit of gas is small, so the gas cylinders must be frequently replaced.

JT systems utilizing a mixture of gases, rather than a pure gas, represent a significant advance in cryosurgical probe technology. The pressure required by a Mixed-Gas Joule-Thomson (MGJT) system is much lower than for a pure gas JT system. Typically, the supply pressure for a MGJT system is 1.5 MPa or 200 psi - an order of magnitude smaller than pure gas systems. Therefore, it is possible to recover the low-pressure mixture leaving the probe and recompress it using a small, portable compressor placed in the operating room. MGJT systems are closed systems that offer the considerable advantage of not using a consumable working fluid; this advantage reduces the hardware, floor space, logistical and ventilation requirements, and expense associated with a procedure. Brodyansky et al. [6] showed that MGJT systems can provide substantially more cooling per unit mass than pure gas JT systems, which leads to a relatively compact and convenient device that is more appropriate for a clinical environment. The thermodynamics underlying the MGJT cycles is discussed in Section 1.2 along with associated configurations suitable for use in a cryoprobe.

The current clinical limitations on the use of cryosurgery are primarily related to the cryoprobe technology itself. For treatments that cover large regions deep within the body, current cryoprobe technology requires that multiple probes be inserted and precisely positioned in order to ensure complete cell death. A single probe with more power in the same geometric envelope is desirable as it is less invasive and more easily controlled. The most recent advancement in cryosurgical probe technology, multi-stage MGJT cycles, addresses this need by improving the underlying thermodynamic cycle. Multi-stage MGJT cycles are used to divide the large temperature range that must be spanned (from room temperature to approximately 140 K) into two smaller temperature stages that can each be addressed using a more compact system. The result is a probe that can provide more refrigeration for a given cryoprobe size.

1.2 MGJT cycles and cryoprobes

Figure 3 provides a schematic of a single-stage MGJT cryoprobe configuration, and Figure 4(a) shows the primary components in the single-stage MGJT thermodynamic cycle, including numbered thermodynamic states. The compressor and aftercooler deliver high-pressure and approximately room-temperature gas mixture to the recuperator at state 3. The recuperator is a Giaque-Hampson-type heat exchanger, that is, a finned tube, helically coiled around a mandrel, along with a flow-directing outer sheath. The high-pressure mixture is cooled by the returning low-pressure stream in the recuperator; this heat

exchange process enables the cycle to efficiently provide cooling at low temperatures. Isenthalpic expansion across the expansion device (capillary tube, orifice, etc.) reduces the mixture temperature to the lowest temperature in the cycle at state 5. The heat removed from the tissue ($\dot{Q}_{load}$) is then applied to the flow stream at the cryoprobe tip (represented in Figure 4(a) as the load heat exchanger); the temperature after the tip (T_6) is typically referred to as the load temperature. The low-pressure mixture then flows through the recuperator and finally returns to the compressor for recovery. The working fluid in the MGJT cycle is typically a Hydrocarbon (HC) or Synthetic Refrigerant (SR) based blend, where the balance gases are noble gases such as nitrogen, krypton, or argon. As discussed in Section 0, the mixture enters and exits the base of the cryoprobe near room temperature; therefore, the mixture can be transported to and from a remotely located compressor via plastic tubing that can be small, flexible, and un-insulated.

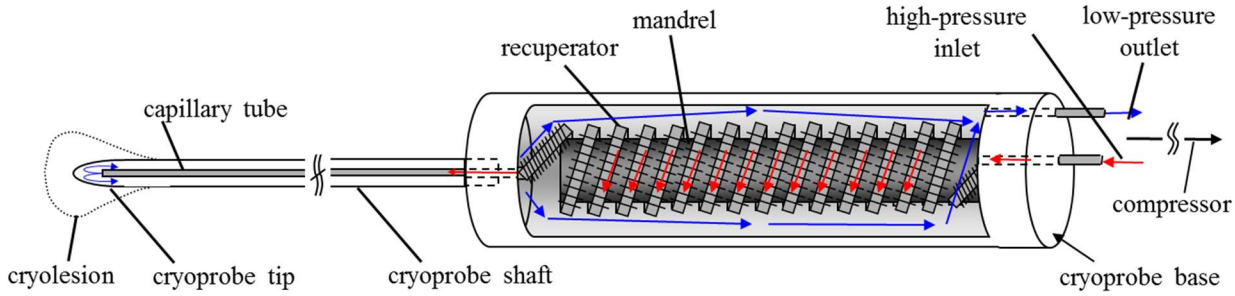

Figure 3: Schematic of a single-stage MGJT cryoprobe.

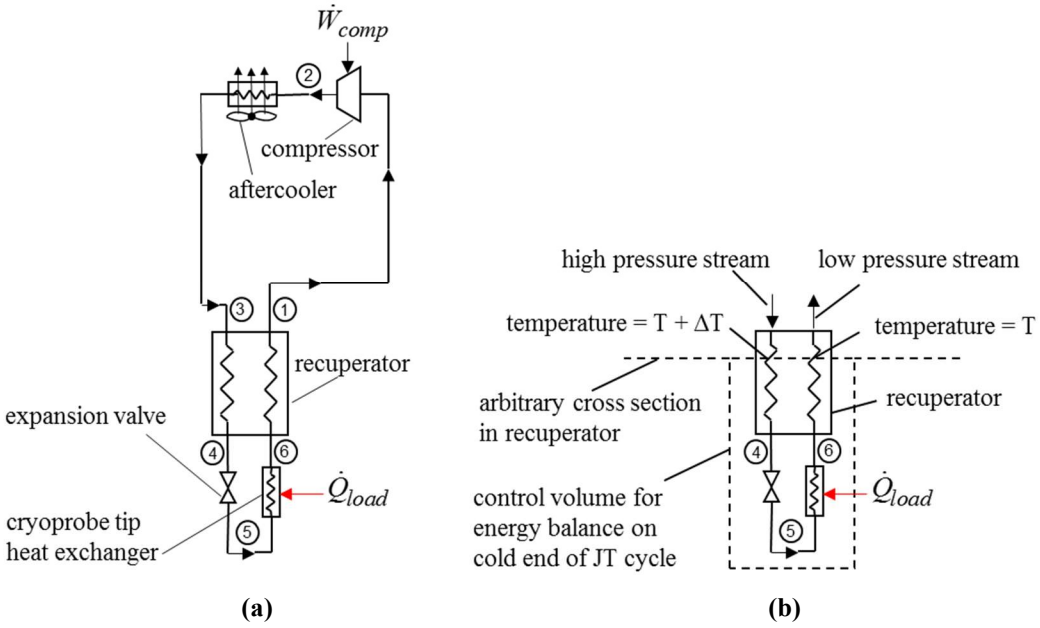

Figure 4: (a) Schematic of single-stage MGJT refrigeration cycle, and (b) control volume around cold end of JT cycle

The refrigeration capacity of a JT cycle is fundamentally limited by the Joule-Thomson effect associated with the working fluid. The capacity can be computed by performing an

energy balance on a control volume that encloses the cold end of the cycle. Figure 4 (b) shows a control volume that passes through an arbitrary location in the recuperator and encloses the expansion device and load head exchanger. The energy balance shows that the refrigeration load is equal to the enthalpy difference between the two streams at any-cross section in the heat exchanger:

$$\dot{Q}_{load} = \dot{m}\left[enthalpy\left(P_{low}, T, \bar{y}\right) - enthalpy\left(P_{high}, T + \Delta T, \bar{y}\right)\right] \tag{1.1}$$

where $\dot{m}$ is the mass flow rate, P_{high} and P_{low} are the discharge and suction pressures associated with the compressor (neglecting pressure loss in the recuperator), T is the temperature of the low-pressure stream at the location of the control volume, ΔT is the temperature difference between the streams at the cross section, and $\bar{y}$ is a vector of the molar concentrations of each component in the gas mixture.

In the limit that the recuperator conductance is infinitely large (i.e., the recuperator is providing the maximum possible rate of stream-to-stream heat transfer), the temperatures of the fluid streams will coincide (i.e., ΔT in Equation (1.1) will approach zero) at some location in the recuperator; this location is commonly referred to as the pinch point. The possible pinch points are evaluated by computing the isothermal enthalpy difference (Δh_T), which is the enthalpy difference between the high- and low-pressure streams at the same T, over the temperature range of the recuperator (T_3 to T_6). The minimum Δh_T occurs at the temperature corresponding to the pinch point, and equals the maximum possible unit refrigeration.

$$\frac{\dot{Q}_{load,\max}}{\dot{m}} = \min\left(\underbrace{\left[enthalpy\left(P_{low}, T, \bar{y}\right) - enthalpy\left(P_{high}, T, \bar{y}\right)\right]}_{\Delta h_T} for\ T = T_3\ to\ T_6\right) \tag{1.2}$$

The Δh_T values are readily evaluated using a pressure-enthalpy (P-h) chart for the working fluid. Figure 5(a) shows a P-h chart for pure nitrogen. Also shown in Figure 5(a) is Δh_T evaluated for a cycle operating between 1000 kPa and 100 kPa at several different temperatures. Notice that the 100 K isotherm passes through the vapor dome and therefore Δh_T is quite large at this temperature. However at higher temperatures such as 150 K and 200 K, nitrogen exhibits behavior that is approaching ideal-gas behavior and therefore Δh_T is very small. This behavior is typical of any working fluid; Δh_T tends to be large only near the vapor dome where real-gas effects govern fluid behavior. The recuperator must nominally span the temperature range from 290 K (warm inlet of recuperator) to 140 K (load temperature – recuperator cold inlet) for a single-stage cryosurgical system. Therefore, the minimum Δh_T will occur at the warm end of the recuperator and will significantly restrict the refrigeration capacity of the cycle.

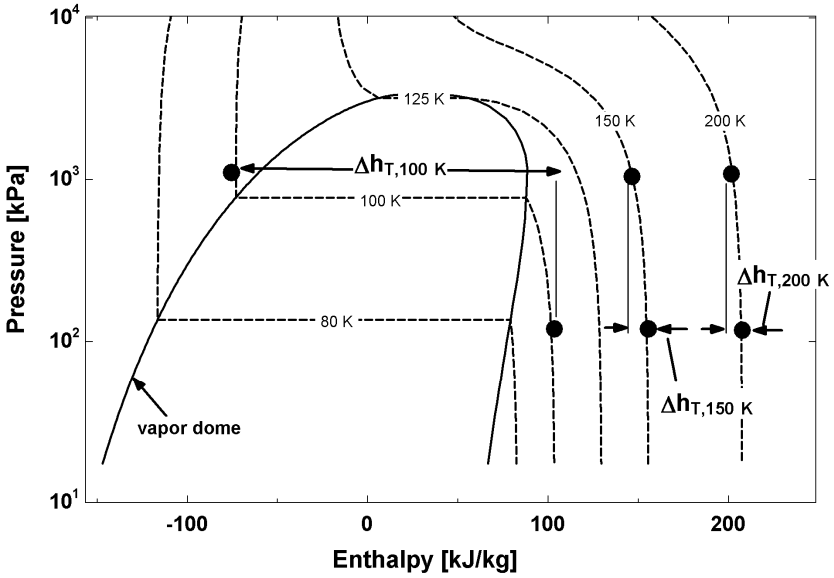

Figure 5: Pressure-enthalpy chart for nitrogen.

The JT cryoprobe requiring the smallest mass flow rate for a desired cooling power would operate within the vapor dome of the working fluid; however, the recuperator temperature span that is required far exceeds the span of the vapor dome of any single-component working fluid. The vapor dome associated with a zeotropic mixture of gases typically extends over a larger temperature range, corresponding to a temperature that is near the lowest normal boiling point of the components, to one that is near the highest normal boiling point of the components. The use of zeotropic gas mixtures therefore significantly extends the temperature range over which Δh_T is large. Figure 6 shows a *P-h* chart for an optimized seven-component mixture consisting of nitrogen, methane, ethane, propane, isobutene, isopentane, and argon. The Δh_T is evaluated at 1000 kPa and 100 kPa, the same values for the nitrogen analysis. The values of Δh_T at warmer temperatures are much larger for the mixture because it remains in the vapor dome. The Δh_T is shown as a function of temperature for the two working fluids in Figure 7; the refrigeration effect (i.e. minimum Δh_T) is 50 times greater for the mixture. Cycles that use mixtures can therefore be significantly more powerful and more practical for cryosurgery.

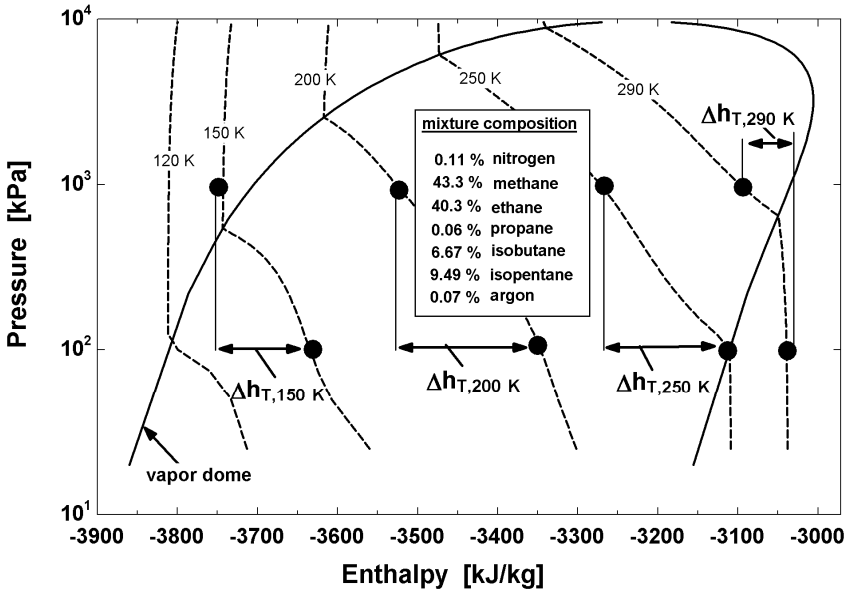

Figure 6: **Pressure-enthalpy chart for an optimized 7-component gas mixture.**

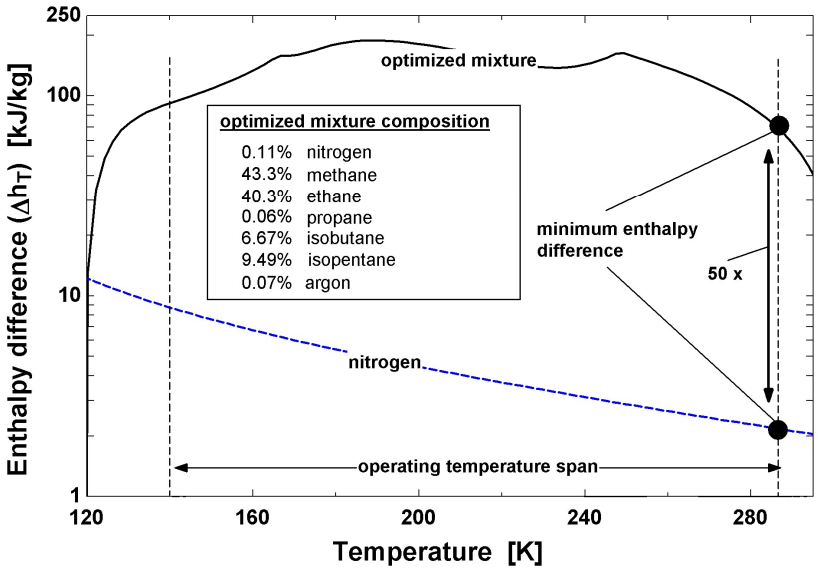

Figure 7: **Comparison of isothermal enthalpy difference for nitrogen, and an optimized 7-component mixture.**

1.3 MGJT cryoprobe with precooling

The MGJT cycle can be configured to provide even greater refrigeration power, using the same-sized cryoprobe, with the addition of a precooling stage (e.g. a 2-stage system). Figure 8 shows the physical integration of a precooled MGJT cycle with a cryoprobe, and Figure 9 provides a cycle schematic of the primary components including numbered thermodynamic states. The 1st stage is a conventional vapor-compression cycle that operates with a single component synthetic refrigerant and precools the high-pressure gas mixture in the 2nd stage JT cycle before it enters the recuperator. The probe configuration

is otherwise the same as in the single stage system where the MGJT cycle provides refrigeration ($\dot{Q}_{load}$) at the tip at the load temperature, T_7.

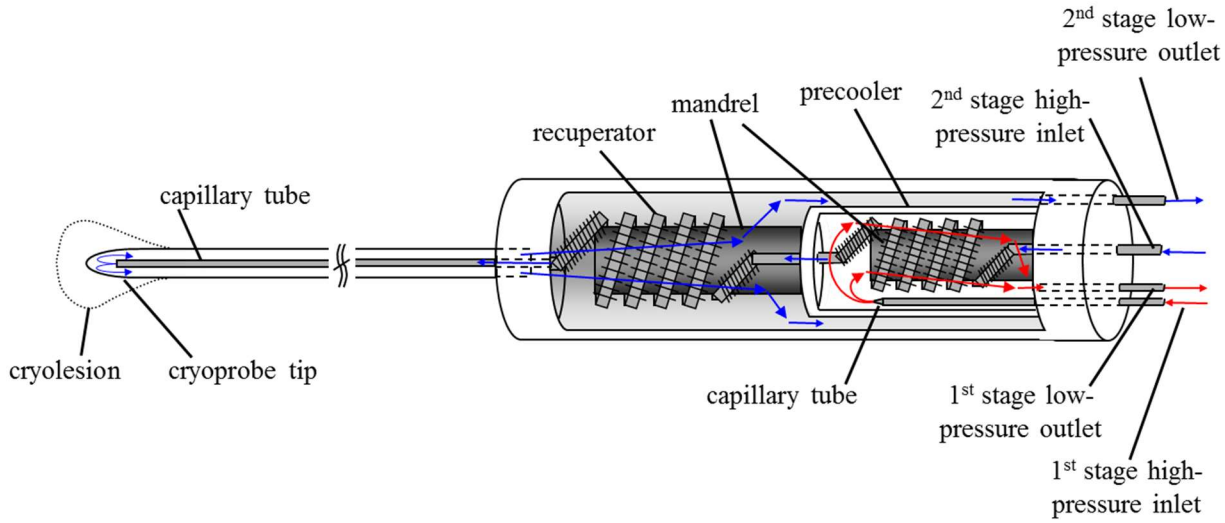

Figure 8: **Schematic of a precooled MGJT cryoprobe.**

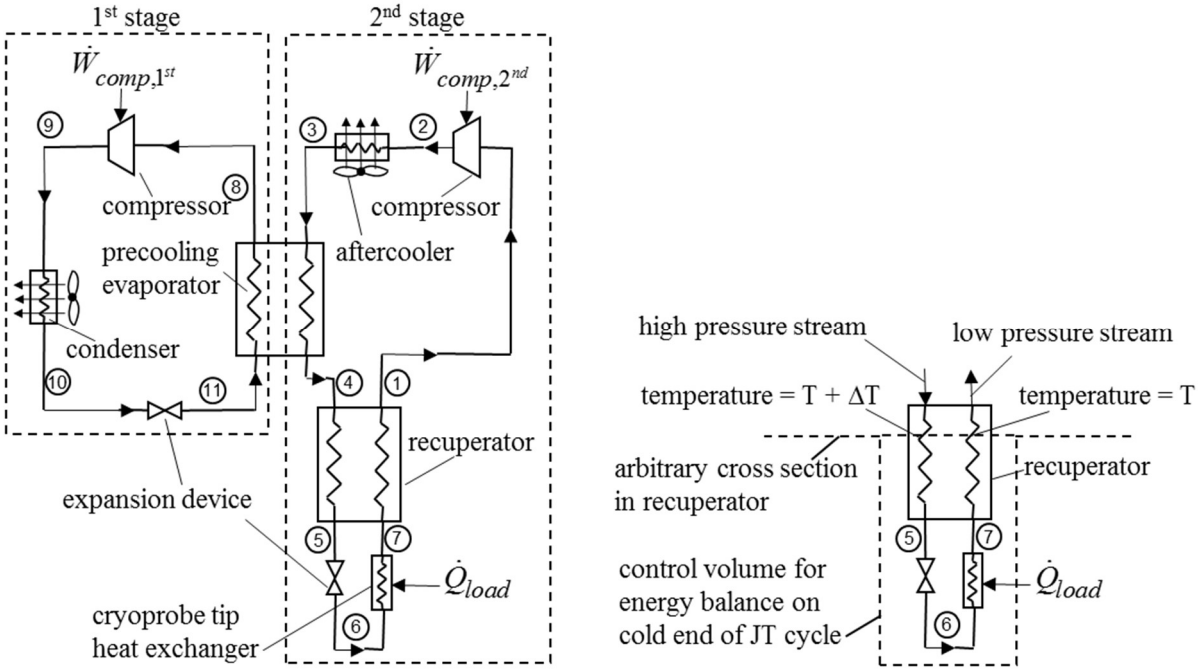

Figure 9: **(a) Schematic of precooled MGJT cycle and (b) control volume around cold end of the MGJT cycle**

The refrigeration effect for this cycle is computed using the same technique as described in Section 1.2. A control volume on the cold end of the 2nd stage of the JT cycle that passes through an arbitrary location in the recuperator is shown in Figure 9(b). The energy balance shows that the flow-specific refrigeration load is equal to the enthalpy difference between the two streams at any cross section in the heat exchanger:

$$\dot{Q}_{load} = \dot{m}_{2^{nd}} \left[enthalpy\left(P_{low,2^{nd}}, T, \bar{y}_{2^{nd}}\right) - enthalpy\left(P_{high,2^{nd}}, T+\Delta T, \bar{y}_{2^{nd}}\right)\right] \tag{1.3}$$

where $\dot{m}_{2^{nd}}$ is the mass flow rate in the 2nd stage, $P_{low,2^{nd}}$ and $P_{high,2^{nd}}$ are the suction and discharge pressures associated with the 2nd stage compressor (neglecting pressure loss in the recuperator and precooler), and $\bar{y}_{2^{nd}}$ is a vector of molar concentrations of each component in the 2nd stage fluid mixture. Again, the maximum achievable refrigeration load per unit mass flow rate is computed as the minimum value of the isothermal enthalpy difference over the range of temperature spanned by the recuperator:

$$\frac{\dot{Q}_{load,\max}}{\dot{m}_{2^{nd}}} = \min\left(\left[enthalpy\left(P_{low,2^{nd}}, T, \bar{y}_{2^{nd}}\right) - enthalpy\left(P_{high,2^{nd}}, T, \bar{y}_{2^{nd}}\right)\right] for\ T = T_4\ to\ T_7\right) \tag{1.4}$$

The mixture optimized for the single-stage MGJT cryoprobe, in Section 1.2, provides a substantial amount of refrigeration over a large operating temperature span. However,

there is a tradeoff between the maximum cooling power that can be provided and the temperature range that must be spanned by the recuperator. For example, consider two different 7-component mixtures that could be used in the JT cycle where the load temperature is 140 K and the high and low pressures are 1000 kPa and 100 kPa. The composition of mixtures A and B have been optimized to produce the maximum JT effect over two different temperature spans, but both mixtures have the same constituents: nitrogen, ethane, methane, propane, isobutane, isopentane, and argon. The mole fractions of these constituents are listed in Table 1. Mixture A is the mixture presented in Section 1.2 that was optimized for the single-stage MGJT cryoprobe with a recuperator temperature span of 290 K to 140 K. Mixture B is optimized for a smaller recuperator temperature span of 238 K to 140 K, which is typical of a JT cycle with some precooling that lowers the recuperator hot inlet temperature to 238 K. Figure 10 shows that the maximum cooling effect (i.e., the minimum value of the isothermal enthalpy change) over the temperature span for mixture A is 73 kJ/kg, whereas the maximum cooling effect for mixture B over its temperature span is 115 kJ/kg. Therefore, by using a 2-stage system to reduce the temperature range that must be spanned by the recuperator in a MGJT system, it is possible to select a mixture that achieves a significant increase in the amount of mass flow specific refrigeration provided at the tip of the cryoprobe.

The benefit of precooling must be evaluated based on whether the increase in cooling power outweighs the increase in overall cryoprobe size and the additional complexity associated with the precooling heat exchanger. A surgically-useful cryoprobe will provide a large amount of cooling while still being physically small and therefore surgically ergonomic, minimally invasive, and easy to control. Cryosurgical procedures utilizing a single probe with a high tissue freezing capacity (rather than multiple probes used to simultaneously target a tissue mass) can be carried out more quickly and planned with greater precision. In a single-stage system, the recuperative heat exchanger is rigidly coupled to the shaft of the cryoprobe as shown in Figure 3, and therefore affects the overall cryoprobe size. In the two-stage system, both the recuperative and precooling heat exchangers are coupled to the cryoprobe, as shown in Figure 8. Figure 11 shows the locations of the two heat exchangers for a precooled MGJT probe. The photo shows that the size of the handheld probe is largely determined by the size of the heat exchangers. The size of the heat exchangers is approximately determined by their conductances, so the most appropriate figure of merit for comparing the compactness of different cycles is the ratio of refrigeration load to the total heat exchanger conductance ($\dot{Q}_{load}/UA$). The heat exchanger conductance of the two-stage system includes the recuperator and precooler; the conductance of the single-stage system only includes the recuperator. The precooled MGJT cycle substantially increases the overall $\dot{Q}_{load}/UA$ [7]. The tradeoff is a larger compressor displacement, which is an acceptable penalty since the compressors are remotely located (provided that the overall probe system remains portable). For example, a 50 % to 60 % increase in $\dot{Q}_{load}/UA$ can be achieved with a 25 % increase in compressor displacement, using a precooling temperature of 235 K.

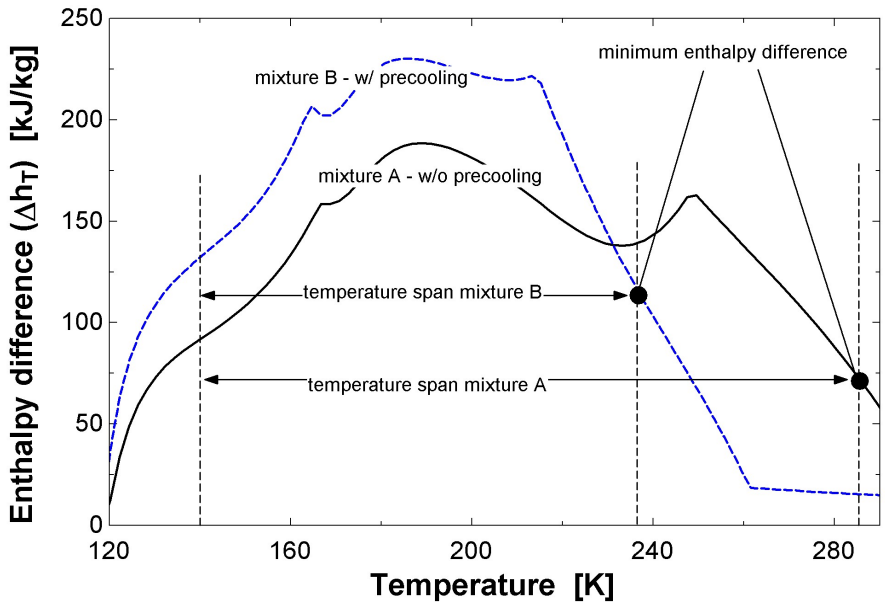

Figure 10: **Enthalpy difference of the high (1000 kPa) and low (100 kPa) pressure streams in the recuperator as a function of temperature for two mixtures. The mixtures are optimized to produce the largest cooling effect across two different temperature spans: Mixture A 140 K to 290 K, and Mixture B 140 K to 238 K.**

Table 1: Mixture operating temperatures and compositions.

	Mixture A	**Mixture B**
Low Temp	140 K	140 K
High Temp	290 K	238 K
Nitrogen	0.11 %	0.01%
Methane	43.30 %	50.10 %
Ethane	40.30 %	39.30 %
Propane	0.06 %	1.17 %
Isobutane	6.67 %	9.38 %
Isopentane	9.49 %	0.01 %
Argon	0.07 %	0.03 %

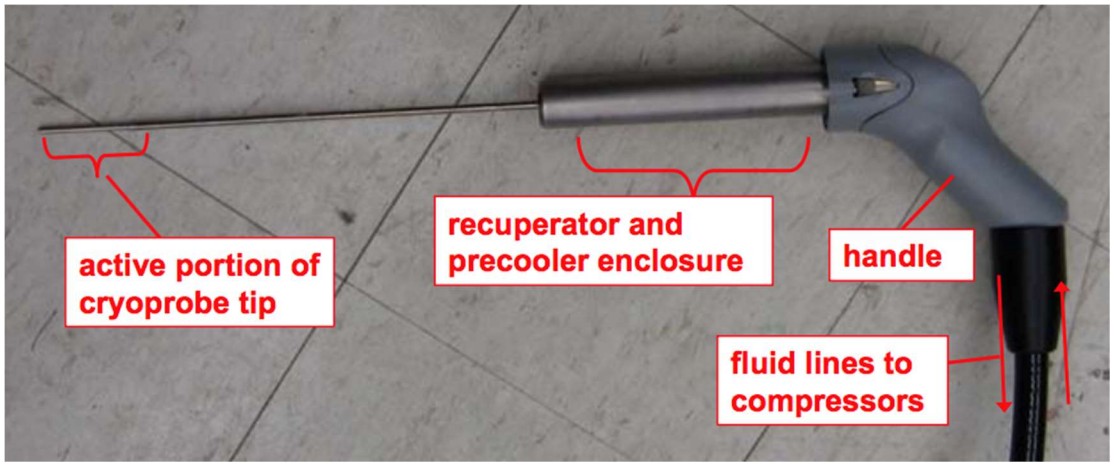

Figure 11: Photograph of a precooled MGJT cryoprobe.

1.4 Commercial options for cryo-ablation systems

At the time of writing, we were able to identify eight U.S. companies providing catheter-based cryo-ablation products for treating cancer tumors (prostate, kidney, liver, breast, etc.), atrial fibrillation, or diseased endometrial lining of the uterus. The assortment of commercial products mirrors the various types of fluid-flow options described in Sections 0 through 1.3; two of the eight utilize liquid nitrogen pressurized to 0.15 MPa as the working fluid, two utilize argon gas pressurized to slightly higher than 20.0 MPa, two use N_2O (nitrous oxide) pressurized to 5.16 MPa, and two utilize the lower pressure MGJT approach.

Both Sanarus and IceCure Medical utilize a supply of liquid nitrogen to produce cooling for cryo-ablation of breast tumors, and guide the position of the cryoprobe with the help of ultrasound imaging. The probe is inserted through a small (3 mm) incision, after which the slightly pressurized liquid nitrogen is allowed to flow through the probe. Thermal insulation and/or heating along most of the probe's length localizes the cooling at the probe tip where the ice ball is formed. The low-pressure nitrogen return flow is exhausted through a connection at the base of the probe and out through the clinic's or hospital's scavenging system.

Two companies, Galil Medical and Endocare, a division of Health-Tronics, use an alternating flow of room-temperature pressurized argon and helium gas to respectively cool and re-warm the probe for alternating freeze-thaw cycles. Because the JT inversion temperature for helium gas is well below room temperature (~44 K), the supply of room temperature helium gas at 11.7 MPa flowing through the same cryoprobe tip where the argon had produced cooling, *warms* (rather than cools) on expanding and causes the tip to return to room temperature. The CryoCare® CS system by Health-Tronics and the Visual-ICE® system by Galil Medical combine the cryo-ablation catheters with thermocouples and ultrasound visualization to monitor the cool-down, ice ball-formation, and warm-up processes. The flexibility of the system allows a selectable cold tip temperature, and the simultaneous use of up to 7 probes to increase the locality of the ice ball.

N_2O provides another option as the working gas in the JT cryo-catheter. Medtronic's Artic Front Advance™ Cardiac Cryo Ablation catheter system and Atricure's CryoICE system are both used to treat atrial fibrillation and utilize N_2O as the working fluid. In most medical applications using N_2O, the fluid is stored at room temperature at a pressure of 5.16 MPa, in which condition it exists as a saturated liquid. As gas is extracted from the storage cylinder, the mass of liquid decreases, but the pressure remains constant until the liquid is gone. Upon expanding to atmospheric pressure (~100 kPa), the gas temperature drops to near 193 K, readily producing a cold zone or ice ball at the catheter tip. Both vendors promote the slow thawing process that occurs after the gas flow is halted as a beneficial method for killing the unwanted cells, noting that a rapid thaw increases the chance of cell survival (a rapid-thaw technique has long been utilized as a treatment to minimize the effects of frostbite).

The primary cryo-ablation product available through Cooper Surgical, Her Option®, uses a blend of non-CFC coolants in a precooled MGJT cycle, where the components are non-toxic, non-flammable, and non-corrosive. The Her Option® system is used to ablate the endometrial lining of the uterus in pre-menopausal, post-child bearing women who are experiencing excessive bleeding due to benign causes. The cooling technology is the same as the precooled MGJT cryoprobe developed by American Medical Systems shown in Figures 8, 9, and 11. The low pressure afforded by the MGJT approach allows the system to operate in the closed cycle described in Section 1.3, with nominal discharge and suction pressures of 1.5 MPa and 0.2 MPa, respectively. Because the mixed-gas working fluid can be circulated indefinitely it requires no re-supply, a convenient feature that stands in contrast to all the other commercial products. A disposable sheath with a conductive tip is used for each procedure; an electric heater is integrated with the sheath for warm-up cycles. Visualization is accomplished via ultrasound, and the warm-up process typically takes about two minutes. The complete system hardware including the two compressors, controller, and probe is housed in a convenient roll-around unit with outer dimensions of 66 cm tall by 69 cm deep by 36 cm wide. The self-contained package is engineered to provide an exclusively in-office, safe, and effective treatment.

In their Frigidtronics® Cryo-Plus system, Cooper Surgical also offers an array of cryoprobes that utilize a N_2O approach for cryo-ablation of cervical or prostate tumors.

1.5 Construction features

In most cases the cryoprobes used for ablation are fairly simple in construction. Commercial versions avoid designs reliant on vacuum jackets because of the expense to fabricate and guarantee the integrity of such a feature. Systems with a single fluid, such as liquid nitrogen or N_2O, require no recuperative heat exchanger. The simple isenthalpic expansion through the JT orifice at the catheter tip from the supply pressure to near ambient pressure provides a sufficient decrease in temperature to enable formation of an ice ball. Thus, the single-gas version of the cryoprobes are comprised of a concentric set of tubes, with the inner tube providing the flow path for the high-pressure supply, the outer

tube providing the flow path for the low-pressure return, and the tip of the tube defining the location for the orifice where the pressure drop and temperature drop occur.

With liquid nitrogen as the working fluid, the concentric tubes are rigid; the outer tube is typically stainless steel, whereas the inner tube is a low-thermal-conductivity material, such as polyether ether ketone (PEEK), which is compatible with the pressures and temperatures involved. Methods to turbulate the return flow enhance the heat exchange between the cold fluid at the probe tip and the surface of the outer tube to form the ice ball (Figure 11). Various methods of warming the return gas, such as an electric heating element, are used to prevent condensation on the exhaust line.

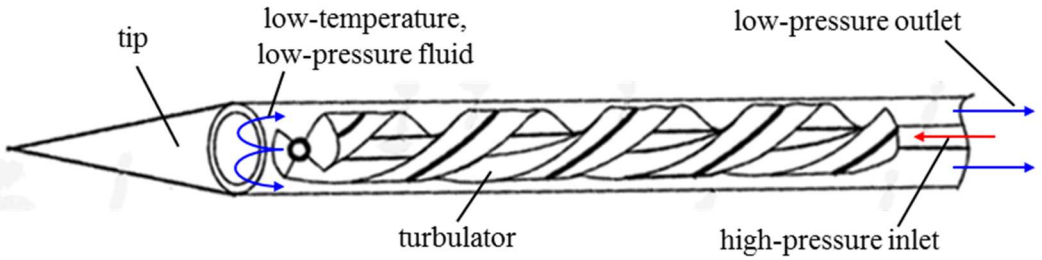

Figure 11. Example of internal configuration to enhance turbulent heat transfer between the return flow and the outer wall [8].

The typical outer diameter of cryoprobes is a few millimeters. Examples of rigid and bendable cryoprobes supplied by Atricure are shown in Figures 12(a) and 12(b). The simple tube-in-tube configuration allows for a section with bellows or malleable metal walls that in turn enable a bendable design; this is useful for applications requiring a particular angle of entry into the body or angle of contact with the patient's tissue.

(a)

(b)

Figure 12. Atricure Cryoprobes: (a) rigid, (b) bendable. Both provide a 10 cm freeze length and utilize N_2O as the working fluid.

Fully flexible versions of the cryoprobe, such as those used for treating atrial fibrillation, are also simply constructed with tube-in-tube designs using materials such as nylon that can easily bend, and are compatible with the inside lining of blood vessels. In such cases, the cryoprobe diameter is approximately 3 mm, while its length may extend as long as 1.8 m. This slender and long configuration allows the probe to be inserted an incision in the femoral artery, directed through blood vessels, and finally located inside the heart. The pressurized N_2O supply gas expands through an orifice at the distal (far) end of the inner

tube producing cooling at the tip of the cryoprobe. Heat exchange between the cooled gas and the tissue surrounding the probe results in the ice ball formation at that location. The cold region is limited to the distal end of the probe by using an insulating sheath or a heating element in the return flow.

For systems using a room temperature high-pressure gas supply, such as argon, the probe is comprised of a Giaque-Hampson-type heat exchanger, where the finned tube high-pressure gas supply line is helically coiled around a mandrel, and an outer sheath directs the return flow. The high-pressure supply flows through the inside of the helically wound finned tube. After expanding through an orifice at the tip of the probe, the gas flows back through the space between the coiled tube and the outer wall of the probe toward the base of the probe.

The dimensions and insulated length of the outer sheath can be designed to achieve various-shaped ice balls. For example, a sheath with insulation extending over the full length of the coiled heat exchanger, as shown in Figure 13, concentrates the cooling effect at the tip of the probe, thereby forming a spherical ice ball. Such a shape is preferred for treating breast tumors.

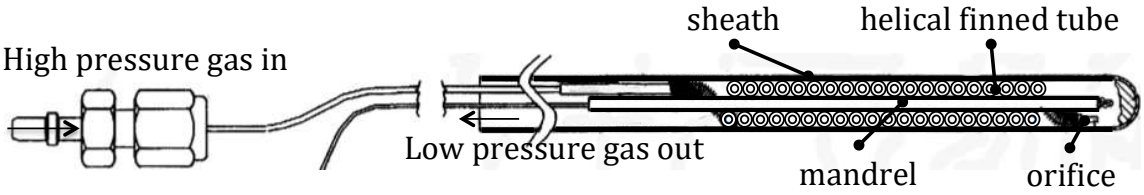

Figure 13. Inner configuration details of a cryoprobe for treating breast tumors

On the other hand, a sheath insulation that extends axially only part of the way from the base will result in an elongated cylindrical ice ball, which is best for treating liver tumors. Additional variations on this design, including two co-wound parallel gas supply tubes and different locations for the orifice, are detailed in reference [8]. The pressurized room temperature helium gas, used for the warming/thawing process, may either flow through the same tube as the cooling gas (argon) or through the second of the two parallel gas supply tubes.

1.6 Precautions

Two precautions typically accompany the use of cryo-ablation systems – ensuring the absence of any gas leaks before using the probe, and making sure that the probe is detached from the ice ball before removing it. Both Endocare and Galil include detailed precautionary instructions that each catheter must be pre-tested to ensure no gas leaks are present. With the large supply pressures involved in their systems, greater than 10 MPa, such a safety procedure is crucial and to be expected. One patent assigned to Endocare [9] describes a probe including an outer sheath that provides enhanced protection against gas leaks that would result in a gas embolism. The outer sheath fits over the distal end of the probe and attaches to the probe handle so that any gas leak from the cryoprobe is directed back toward the proximal end. A heat conducting fluid/material, such as petroleum jelly,

fills the very narrow gap between the inner wall of the sheath and outer wall of the probe to maintain the probe's primary function of creating an ice ball. In one variation of the design, a tube running from the gap between the sheath and probe to a pressure sensor at the proximal (handle) end of the cryoprobe allows the operator to identify any pressure increase from a gas leak, an occasion where the operator would remove the probe. Systems that include two gases (e.g., argon and helium) to apply the freeze/thaw cycle also prescribe a pre-test of the gas connection. Lastly, the MGJT system utilized by Cooper Surgical also prescribes a pretest to verify the freeze cycle performance of the probe, and a warning against bending the probe to avoid creating a gas leak.

The literature provided by each of the companies gives explicit warnings to not remove the cryoprobe while it is cold. The obvious reason is to avoid tearing any of the tissue adhered to the probe via the ice ball or the cold (< 0 ˚C) probe surface. A variety of approaches are used to re-warm tissue after the ice ball is formed, including: flooding the area with a warm saline solution or other suitable liquid, utilizing the warming effect upon expansion of a flow of pressurized helium gas, or using heater elements to heat the probe or a flow of (low-pressure) gas through the probe. In many instances, operating instructions prescribe multiple freeze-thaw cycles to promote complete cell death in the target area.

1.7 Future direction

At the time of this writing, the existing literature regarding the use of cryo-ablation for treating cancer and other medical problems exudes a very promising future. Reports indicate a high success rate for the procedure. Furthermore, the *interactive MR Imaging Guided Intervention* (iMR-IGI) approach being developed by Marvel Medtech combines MRI imaging with cryo-ablation to identify and preemptively treat MRI screening-detected breast tumors in their earliest-detectable stages. Such preemptive treatment of breast lesions with cryotherapy, even before a cancer diagnosis, may trigger a cancer immunity response by the body, as explained by the first beneficiary of breast cancer cryo-ablation treatment in the United States, Laura Ross-Paul. The Sandra and Edward Meyer Cancer Center in New York reports one reason for such an interesting expectation (https://meyercancer.weill.cornell.edu/news/2016-10-19/cryoablation-freezing-away-breast-cancers):

> *Besides the no-pain, no-scarring advantages, there's another potential perk with this technique: "The possibility that freezing a cancer and leaving it in the body to be absorbed may stimulate an anti-cancer immune response," explains Dr. Michael Sabel, chief of surgical oncology at the University of Michigan Hospital in Ann Arbor, who also participated in the study. "This has been demonstrated in mice and we are now studying this in patients."*
>
> *With metastatic breast cancer, in particular, "we have found that if we ablate the original cancer, the metastatic disease goes away in a mouse model," Simmons explains. "What we think is happening is the cryoablation makes the cells burst and they release all that cancer DNA into the system. The body's immune system almost acts as an auto-vaccine against the cancer," which could help reduce the chances of a recurrence as well.*

Marvel Medtech further reports that similar results are being found with humans:

Cryotherapy – destroying a cancer tumor by freezing – is known to induce a natural anti-tumor immune response [10] that can prevent recurrence and spreading of the disease. Beginning in the early 2000s, research efforts in the U.S. to prove cryotherapy an effective breast cancer treatment have shown promise, but progress here has been slow. Parallel efforts in China have shown greater success, with some 4000 patients treated with cryotherapy and follow-up immunotherapy to boost the anti-tumor immune response. A leading breast cancer research investigator in the U.S., citing recent successes in their understanding of targeted immunotherapy, has predicted that surgical treatment of breast cancer will give way to "Cryoimmunotherapy" as the new breast cancer standard of care. However, at the current pace of progress, it will take at least several more years to achieve this new state of breast healthcare.

A *"natural anti-tumor immune response"* as a result of cryo-ablation and *"cryo-immunotherapy as a new breast cancer standard of care"* suggests a very successful future for such procedures. These treatments, along with the ones targeting other types of cancer and atrial fibrillation, are a foundation for an auspicious future for cryo-ablation in general, as well as the Joule-Thomson cooling system upon which they are based.

1.8 References

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